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A Phase II Feasibility Study of Oral Etoposide Given Concurrently with Radiotherapy Followed by Dose Intensive Adjuvant Chemotherapy for Children with Newly Diagnosed High-Risk Medulloblastoma; COG Protocol POG 9631, A Report from the Children's Oncology Group

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Abstract

Background—Children with high-risk medulloblastoma historically have had a poor prognosis. The Children's Oncology Group completed a Phase II study using oral etoposide given with radiotherapy followed by intensive chemotherapy.

Procedure—Patients enrolled on study had high-risk disease defined as $\geq 1.5\text{cm}^2$ of residual disease post-surgery or definite evidence of central nervous metastasis. All patients underwent surgery followed by radiotherapy. During radiation, patients received oral etoposide (21 days on 7 off) at an initial dose of $50\text{ mg/m}^2/\text{day}$ (treatment 1) that was reduced to $35\text{ mg/m}^2/\text{day}$ (treatment 2) due to toxicity. Post radiotherapy, patients received chemotherapy with 3 cycles of cisplatin and oral etoposide, followed by 8 courses of cyclophosphamide and vincristine.

Results—Between November 1998 and October 2002, 53 patients were accrued; 15 received treatment 1 and 38 treatment 2. Forty-seven patients (89%) were eligible. Response to radiation was excellent with 19 (40.4%) showing complete response, 24 (51.1%) partial response and 4 (8.5%) not recorded. The overall 2 year and 5 year progression free survival (PFS) was $76.6\pm 6\%$

and $70.2 \pm 7\%$ respectively. The 2 year and 5 year overall survival (OS) was $80.9\% \pm 6\%$ and $76.6\% \pm 6\%$ respectively. Clinical response post-radiation and PFS/OS were not significantly different between treatment groups. There was a trend towards a difference in 5 year PFS between those without and with metastatic disease ($p=0.072$).

Conclusions—Oral etoposide was tolerable at $35\text{mg}/\text{m}^2$ (21 days on and 7 days off) when given during full dose irradiation in patients with high-risk MB with encouraging survival data.

Keywords

High-risk Medulloblastoma; Oral Etoposide; Irradiation; Pediatric Neuro-Oncology

Introduction

Central nervous system (CNS) tumors as a group make up the most common solid tumors in children. Of these, medulloblastoma is the most common malignant tumor and comprise 9.3% of CNS tumors in the 0 – 14 year old age group and has an incidence rate of 0.49 per 100,000 [1]. Therapy for high-risk medulloblastoma has improved over time from the early 1970s when 5 year survival was around 40% to now being over 60% [1]. The standard of care at Children's Oncology Group (COG) institutions for the treatment of high-risk medulloblastoma in those >3 years of age has usually been and is still craniospinal radiation (CSRT) with concurrent chemotherapy followed by maintenance chemotherapy [2–6].

The Pediatric Oncology Group (POG) previously showed in the 9031 study that the use of chemotherapy either before or after craniospinal radiation was effective in treating high-risk medulloblastoma with a 5 year progression free survival (PFS) of 68.1% and overall survival (OS) 74.6% [6]. POG 9631 was undertaken to evaluate if giving oral etoposide during radiation in combination with post CSRT adjuvant chemotherapy could improve survival. Oral etoposide previously has been used successfully in the treatment of recurrent medulloblastoma but this is the first study to use upfront oral etoposide during radiation in newly diagnosed high-risk medulloblastoma patients [7–10].

Materials and Methods

Patient population

Patients were between the age of 3 and 21, with high-risk medulloblastoma as defined by one of the following: residual disease of $\geq 1.5\text{ cm}^2$ on post-operative CT or MRI performed both with and without contrast, preferably within 72 hours of surgery, or between day 10 and 21 after surgery; definite evidence of CNS metastases at diagnosis (M1-M3 by Chang classification) or presence of extraneural metastasis confirmed histologically (M4) [11]. Patients had to have no previous radiotherapy or chemotherapy other than corticosteroids. Other eligibility criteria included adequate physiologic functions defined as ANC $\geq 1,500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, serum creatinine $< 1.7\text{ mg}/\text{dL}$ or creatinine clearance $> 70\text{ ml}/\text{min}/1.73\text{ m}^2$, SGPT < 5 times normal and bilirubin $< 1.5\text{ mg}/\text{dL}$. Informed consent was obtained as per institutional guidelines and patients began therapy within one month of definitive surgery. Pregnant and breast feeding women were not eligible for this study. Radiology was centrally reviewed by the principal investigator, the study neuro-radiologist

and the study radiation oncologist. Pathology was reviewed centrally, however specific histological data for each tumor is no longer available. The study was approved by an institutional review board at each participating site and all subjects or their parents signed informed consent.

Study design

The treatment schema for POG 9631 is given in Supplemental Figure S1. All patients underwent surgical debulking followed by craniospinal radiation (CSRT) with boost to the posterior fossa. Sites of metastatic disease were given an additional RT boost of 5.4 Gy. During CSRT, patients received daily oral etoposide on days 1–21 and days 29–49 dosed at 50mg/m²/day (Treatment 1). After 12 patients there was a stopping rule to allow assessment of toxicity and due to two episodes of grade IV dysphagia the dose of etoposide was decreased to 35mg/m²/day for subsequent patients (Treatment 2). Three additional patients were already enrolled before the change was made and so a total of 15 patients were assigned to receive Treatment 1. Four weeks after completion of chemoradiotherapy, patients received three courses of monthly intravenous cisplatin 90 mg/m²/day given with oral etoposide on days 1 through 21 (same dose as given during radiation), followed by eight monthly cycles of intravenous cyclophosphamide 1.5 gm/m²/day x 2 days and weekly intravenous vincristine 1.5 mg/m² (days 1, 8, and 15). Granulocyte stimulating factor was administered at 5 µg/kg/day for at least 10 days starting 24 hrs after the last chemotherapy.

Radiation

Radiation therapy was administered to all patients. The dose of radiation to the cranial meningeal fields and spine was 36 Gy in 20 fractions for patients with M₀-disease and 39.6 Gy in 22 fractions for patients with M₁-M₃-disease given as 1.8 Gy fraction per day. The dose to the posterior fossa was 19.8 Gy in 11 fractions for M₀-disease patients and 16.2 Gy in 9 fractions for M₁-M₃-disease patients given as 1.8 Gy fraction per day. Metastases to the brain or spine were boosted with an additional 5.4 Gy in 3 fractions of 1.8 Gy. For diffuse spinal metastasis that could not be included in the planned boost, additional planned target volumes were allowed at the discretion of the investigator. The radiation dosing plan was considered standard of care at the time of study design.

Statistical Analysis

The original objectives of the study were to 1) Estimate response rate and describe toxicities; 2) Compare response rate and toxicity to historical control patients treated on POG 9031 Treatment 2 (RT followed by adjuvant chemotherapy) who would have been eligible for treatment on POG 9631; 3) Estimate 2-year PFS and OS rates; and 4) Evaluate toxicity of adjuvant chemotherapy. Comparisons between groups were compared using Fisher's Exact test. PFS was calculated from the on-study date to the date of disease progression or date of death, and OS to the date of death. Patients who did not experience an event for PFS or OS were censored at their last follow-up date. Survival distributions were estimated using the Kaplan-Meier method and were compared with POG 9631 and POG 9031 using the Log-rank test. The association of age at diagnosis with PFS and OS was investigated using a Cox Proportional Hazards model. The study was powered to detect 20% improvement in the historical POG 9031 objective response rate of 69%.

Response was assessed at the end radiation and again at the end of chemotherapy. A complete response (CR) was defined as disappearance of all detectable tumors by imaging, including spinal imaging, if initially positive, as well as 2 consecutively negative CSF cytologic examinations; with stable or improving neurological status. A partial response (PR) was defined as $\geq 50\%$ reduction in the sum of the products of the maximum perpendicular diameter of all measurable lesions compared to the baseline evaluation, or 2 consecutively negative CSF cytologies and a $<50\%$ reduction in tumor size with no evidence of progression in any lesion or any new lesions; stable or improving neurological status. Stable disease (SD) was defined as $<50\%$ reduction in the sum products of the maximum perpendicular diameters of all measureable lesions, and persistently negative or positive CSF cytology with no evidence of progression in any lesion and no new lesions; stable or improving neurological status. Data was censored in March 2007 and so no further follow-up data is available beyond this point.

Results

Baseline data for the cohort by treatment group is given in Table 1. Between November 1998 and October 2002, a total of 53 patients with newly diagnosed medulloblastoma were accrued. Six patients were declared ineligible (2 did not meet criteria for high-risk disease, 1 did not meet inclusion criteria, and 3 did not follow guidelines related to timing for start of therapy). This resulted in 47 eligible subjects. Thirteen received Treatment 1 and 34 received Treatment 2. The median age of patients was 8.1 years (range 3.2 – 21.2). The cohort was 72% male and 91% Caucasian. The M stages were M0 with $>1.5\text{cm}^2$ residual $n=12$, M1 $n=11$, M2 $n=6$, M3a $n=6$, M3b $n=12$, and M4 $n=0$.

Response to radiation and at end of therapy

Response to therapy according to treatment group and stage are given in Table 2. All patients with reported data regardless of therapy showed at least a PR to radiation. After radiation, there was no difference in the response to therapy between the two etoposide treatments, but there was a significant difference in complete response between those with M0, M1, or M2 disease vs. M3 disease ($p=0.013$). The response at end of therapy was also not different between etoposide treatment groups, but again the number of subjects with complete response was higher in those with M0, M1, or M2 disease vs. M3 disease ($p=0.002$). Progression by end of therapy was higher in etoposide group 2 (14.7%) versus group 1 (7.7%), however this did not reach statistical significance.

Survival

Event free and overall survival information is given in Table 2. The 2 year and 5 year progression free survival for the entire study was $76.65\pm 6\%$ and $70.2\pm 7\%$ respectively. The 2 year and 5 year overall survival was a little better at $80.9\pm 6\%$ and $76.6\pm 6\%$ respectively. Two year and 5 year PFS/OS did not differ between etoposide treatment groups (Figure 1). There was a trend towards a difference in 5 year PFS/OS between those without and with metastatic disease; $p=0.072$ for PFS and $p=0.096$ for OS respectively (Figure 2).

Comparison to POG 9031

Response and survival outcomes were compared to patients treated with POG 9031 [6]. In POG 9031, there were 112 patients of whom 57 were evaluable for response and 73 evaluable for survival. Twenty-six patients were excluded from the comparison because of T3b disease and 13 because of T4 disease with no residual mass and M₀. Objective response (CR+PR) to chemo-radiotherapy was similar between POG 9631 and POG 9031, 91% (43/47) and 86% (49/57) respectively ($p = 0.54$). Two- and 5-year PFS/OS were also not different between those on POG 9631 and POG 9031 (Figure 3). Gender and race were not statistically significantly associated with PFS or OS in either study. Age at diagnosis was associated with PFS and OS in POG 9631, where the risk of disease progression decreases as age at diagnosis increases (p -values are 0.017 and 0.013, respectively). This finding persists even after controlling for M stage [For PFS, age at diagnosis hazard ratio (HR) 0.79 [95% confidence interval (CI) 0.66, 0.096] $p=0.015$ and for OS, age at diagnosis HR 0.75 CI [0.59, 0.94] $p=0.013$. The association between age and progression was not seen in the POG 9031 cohort. (p -values are 0.16 and 0.24, respectively).

Toxicities

Toxicities were as expected and mainly hematological (Table 3) and cumulative toxicities are given in (Supplemental Table S1). During radiation, anemia and neutropenia were more common in etoposide group 1, 3/13 (23%) and 8/13 (62%) respectively versus in etoposide group 2, 1/47 (3%) and 10/47 (29%), however there was no difference in the need for transfusions. In etoposide group 1, there was a high incidence of dysphagia and esophagitis related to radiation 4/15 (26.7%) with this leading to a decrease in the etoposide dose. In etoposide group 2, dysphagia was seen less often 2/34 (5.9%). There was no difference in other gastrointestinal (GI) and renal toxicities between etoposide groups and grade 3 or 4 toxicities occurred sporadically with anorexia, and nausea/vomiting being most common. Infections were rare during radiation and were more common during the more intensive parts of chemotherapy (Table 3). Other serious toxicities that occurred rarely included hemorrhage 2, pericardial effusion 1, syndrome of inappropriate antidiuretic hormone secretion 1, ataxia 4, alternated consciousness 2, and vision changes 1. There have been 13 deaths at the time of censoring, March 2007; 4 were on Treatment 1 and 9 on Treatment 2. One death was due to hemorrhage, one to radiation-induced vasculopathy and one was due to multi-organ failure during bone marrow transplant. All other deaths were due to tumor progression.

Discussion

High-risk medulloblastoma remains a challenging disease to treat but this study was able to achieve good 5 year PFS (70%) and OS (77%) similar to or superior to other contemporary high-risk medulloblastoma trials with PFS ranging from 43%–71% and OS from 52%–82% [2–6,12,13]. In this trial and in others the inclusion of craniospinal radiation and intensive chemotherapy has improved PFS. Specifically it showed similar results to the POG 9031 arm that also gave chemotherapy post-radiation [6].

This is a first pediatric brain tumor study to use oral etoposide during radiation. Oral etoposide was selected based on the experience with relapsed medulloblastoma [7,8]. Chamberlain *et al*, showed that in 1 adult and 7 pediatric patients with relapsed medulloblastoma who received oral etoposide, 5 out of 8 (63%) had either partial response or stable disease that was sustained for a period ranging from 4–10 months[8]. Ashely *et al*. showed in a similar population of pediatric relapsed medulloblastoma subjects that 6 of 7 subjects who received oral etoposide monotherapy had a partial response with the remaining patient having stable disease[7]. In this study, giving oral etoposide during radiation resulted in excellent response rates during radiotherapy with over 40% of subjects showing a complete response and all subjects who have reported data showing at least a partial response. Subjects receiving the higher dose of etoposide (50mg/m²/dose) had a high rate of dysphagia/esophagitis 26.7%, which was considered a dose limiting toxicity, however this was much rarer (5.9%) in the lower dose etoposide group (35mg/m²/dose) and significantly during radiation there were no other dose limiting toxicities in either group. Thus using oral etoposide during radiation is feasible and tolerable, but would need to be evaluated in a larger trial to assess for toxicity before it should be used as standard of care. COG as well as HIT-SIOP have evaluated other therapies during radiation and the standard of care has been to give vincristine weekly during radiation and has had a low complication rate (<5% rate peripheral neuropathy/ileus)[4,14]. Jackacki *et al*, published the results from a Phase I/II COG study for high-risk medulloblastoma that in the superior arm added carboplatin to vincristine during radiation followed by maintenance cyclophosphamide and vincristine which showed nearly the same long-term PFS (71%)/OS (82%) as this study[4]. Radiation induced esophagitis was also seen in this study on the Carboplatin arm as well though in only 3.8% of the subjects, however 14.6% of subjects hit some type of dose limiting toxicity during radiation and there was a high prevalence of ototoxicity [4]. This strategy of adding carboplatin during radiation for high-risk medulloblastoma is being evaluated as a randomized question in a current COG study (ACNS 0332). Another agent that has been shown to be safe to give during radiation in adults is temozolomide and there is pediatric data that has shown it is active against medulloblastoma, however published pediatric toxicity data for this approach is still lacking[15–17]..

This study was not powered to assess the difference in survival between those with M0 with residual disease and those with more extensive metastatic disease, however there was a trend towards higher survival in those with M0 disease with residual over those with more extensive disease. This survival difference was confirmed in the larger POG 9031 trial[6]. This study is limited by not having specific histologic or molecular stratification of tumors. The presence of anaplasia has been shown to be a negative prognostic features in several studies[3,4], and now more recently medulloblastoma have been molecular stratified into groups that also impact survival. [18–20]. This new molecular information at this point is useful for prognostic information, but there is great potential that using it will lead to more specifically targeted drug therapy and so should be considered anytime new medulloblastoma studies are designed. It is an interesting finding that being older at diagnosis was associated with better PFS and OS even when adjusted for M staging. The reason for this finding is not clear as subjects were given the same chemotherapy/radiation

plan regardless of age. Unfortunately this study is too small to investigate if other factors could have contributed to this finding.

In conclusion, this study showed the approach of using oral etoposide with craniospinal radiation followed by intensive chemotherapy is feasible and results in good PFS and OS that is similar to other high-risk regimens and had minimal toxicity at the lower etoposide dose. Thus it may be a reasonable treatment regimen to consider in future trials for newly diagnosed high-risk medulloblastoma patients. Future molecular stratified studies will be necessary to discover for which medulloblastomas this treatment would be most effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations Key

PFS	Progression free survival
OS	Overall survival
CNS	Central nervous system
COG	Childrens Oncology Group
POG	Pediatric Oncology Group
CSRT	Craniospinal radiation
CR	Complete response
PR	Partial response
SD	Stable disease
HR	Hazard ratio
CI	Confidence interval
GI	Gastrointestinal

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Figure 1.

a. Progression free survival is not statistically significant different for the patients treated with 50 mg/m²/Day versus 35 mg/m²/Day, Log-rank test (p=0.54). b. Overall survival was also not statistically significant different for the patients treated with 50 mg/m²/Day versus 35 mg/m²/Day, Log-rank test (p=0.55).

Figure 2.

a. There is trend towards progression free survival being better in those with M0 disease with residual versus patients with M+ disease Log-rank test ($p=0.072$). b. There is also trend towards overall survival being better in those with M0 disease with residual versus patients with M+ disease. Log-rank test ($p=0.096$).

Figure 3.

a. Progression free survival is not statistically significant different for the subjects treated with chemotherapy post radiation on POG 9031 and those treated with either treatment on POG 9631, Log-rank test (p=0.93). b. Overall survival is also not statistically significant different for the subjects treated with chemotherapy post radiation on POG 9031 and those treated with either treatment on POG 9631, Log-rank test (p=0.99).

Table 1**Characteristics of the Cohort by Treatment Group**

Characteristics	Treatment Group 1¹	Treatment Group 2²	Overall
	(N=13)	(N= 34)	(N=47)
Age, years, median (range)	6.2 (3.1–10.5)	8.9 (3.5–21.1)	8.1 (3.2–21.2)
Gender, N (%)			
Male	10 (77)	24 (71)	34 (72)
Female	3 (23)	10 (29)	13 (28)
Race/Ethnicity, N (%)			
Caucasian non-Hispanic	12 (92)	31 (91)	43 (91)
African American	0 (0)	1 (3)	1 (2)
Other/not reported	1 (8)	2 (6)	3 (6)
Disease stage at diagnosis ³			
M ₀	5 (38.5)	7 (20.6)	12 (25.5)
M ₁	4 (30.8)	7 (20.6)	11 (23.4)
M ₂	0 (0)	6 (17.6)	6 (12.8)
M _{3a}	2 (15.4)	4 (11.8)	6 (12.8)
M _{3b}	2 (15.4)	10 (29.4)	12 (25.5)
M ₄	0 (0)	0(0)	0 (0)
Extent of resection			
Gross total resection (100%)	4 (30.8)	0 (0)	4 (8.5)
Near total resection (>95% but <100%)	3 (23.1)	13 (38.2)	16 (34)
Subtotal resection (50–95%)	6 (46.2)	13 (38.2)	19 (40.4)
Partial (10–49%)	0 (0)	4 (11.8)	4 (8.5)
Biopsy (<10%)	0 (0)	3 (8.8)	3 (6.4)
Unknown	0 (0)	1 (2.9)	1 (2.1)
Amount of residual post resection			
None	4 (30.8)	8 (23.5)	12 (25.5)
<1.5cm ²	3 (23.1)	9 (26.5)	12 (25.5)
>1.5cm ²	6 (46.2)	16 (47.1)	22 (46.8)
Unknown		1 (2.9)	1 (2.1)

¹Treatment group 1- Etoposide 50mg/m²/day during radiation

²Treatment group 2- Etoposide 35mg/m²/day during radiation.

³Chang classification: M₀-No evidence of gross subarachnoid or hematogenous metastasis, M₁- Microscopic tumor cells found in CSF, M₂- Gross nodular seeding demonstrated in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles, M_{3a} Gross nodular seeing in the spinal subarachnoid space without evidence of intracranial seeding, M_{3b}- Gross nodular seeding in the spinal subarachnoid space as well as intracranial seeding, M₄- Metastasis outside the cerebrospinal axis.

Table 2

Response to therapy

<u>Characteristics¹</u>	<u>Post radiation Response²</u>	<u>End of therapy response²</u>	<u>2 year PFS/OS³</u>	<u>5 year PFS/OS³</u>
Treatment arm response				
Overall			76.6±6/80.9±6	70.2±7/76.6±6
Complete Response	19 (40.4)	29 (61.7)		
Partial Response	24 (51.1)	7 (14.9)		
Stable Disease/progression/relapse	0 (0)	6 (12.8)		
Unknown/not reported	4 (8.5)	5 (10.6)		
Group 1(Etoposide 50 mg/m2)			84.6±10/84.6±10	76.9±11/84.6±10
Complete Response	6 (46.2)	10 (76.9)		
Partial Response	7 (53.8)	2 (15.4)		
Progression/Relapse	0 (0)	1 (7.7)		
Unknown/not reported	0 (0)	0 (0)		
Group 2 (Etoposide 35mg/m2)			73.5±7/79.4±7	67.5±9/73.4±8
Complete Response	13 (38.2)	19 (55.9)		
Partial Response	17 (50.0)	5 (14.7)		
Progression/Relapse	0 (0)	5 (14.7)		
Unknown/not reported	4 (11.8)	5 (14.7)		
Disease stage at diagnosis				
M0 (N=12)			91.7±8/91.7±8	91.7±8/91.7±8
Complete Response	7 (58.3)	10 (83.3)		
Partial Response	5 (41.7)	0 (0)		
Unknown/not reported		2 (16.7)		
M1 (N=11)			71.4±7/77.1±7 ⁴	62.7±8/71.4±8 ⁴
Complete Response	6 (54.5)	8 (72.7)		
Partial Response	3 (27.3)	0 (0.0)		
Unknown/not reported	2 (18.2)	2 (18.2)		
Progression/Relapse		1 (9.1)		
M2 (N=6)				
Complete Response	3 (50)	4 (66.7)		
Partial Response	3 (50)	0 (0)		
Progression/Relapse	0 (0)	2 (33.3)		
M3a (N=6)				
Complete Response	1(16.7)	1 (16.7)		
Partial Response	4 (66.7)	2 (33.3)		
Unknown/not reported	1 (16.7)	1 (16.7)		
Progression/Relapse		2 (33.3)		
M3b (N= 12)				
Complete Response	2 (16.7)	6 (50)		
Partial Response	9 (75.0)	5 (41.7)		
Unknown/not reported	1 (8.3)	0 (0)		

Characteristics¹	Post radiation Response²	End of therapy response²	2 year PFS/OS³	5 year PFS/OS³
Progression/Relapse	0 (0)	1 (8.3)		
Amount of residual post resection				
None (n=12)			83.3±10/83.3±10	83.3 ±10/83.3±10
<1.5cm ² (n=12)			66.7±13/75.0±12	41.7±13/66.7±13
>1.5cm ² (n=22)			77.3±9/81.8±8	77.3(±10)/77.3±10

¹Date of censor 10/1/2007,

²N (%),

³Progression free survival (PFS)/Overall survival (OS) expressed as %±Standard error),

⁴PFS/OS estimate is for all M+ disease

Table 3

Incidence of Grade 3 or 4 Toxicities on Protocol POG 9631

Toxicity	Course											
	1 ²	2 ³	3	4	5 ⁴	6	7	8	9	10	11	12
# Patients ¹	47	47	47	47	46	42	40	39	39	38	35	31
Hearing dysfunction	2%	0%	17%	6%	2%	7%	3%	5%	5%	0%	0%	3%
Anemia	9%	19%	26%	30%	54%	57%	48%	51%	67%	66%	54%	68%
Need for PRBC transfusion	6%	13%	15%	17%	50%	57%	45%	49%	56%	55%	54%	58%
Thrombocytopenia	0%	9%	6%	11%	76%	57%	70%	69%	49%	76%	57%	52%
Need for platelet transfusion	0%	4%	6%	9%	39%	38%	35%	41%	49%	45%	49%	52%
Neutropenia	38%	51%	47%	38%	63%	64%	75%	69%	77%	84%	80%	84%
Dysphagia	13%	0%	0%	0%	2%	0%	0%	0%	3%	0%	0%	0%
Infection	4%	11%	0%	2%	26%	17%	15%	18%	23%	24%	20%	16%
Neuropathy ⁵	0%	0%	0%	0%	13%	5%	8%	10%	13%	16%	14%	10%

¹ Patients censored at times of relapse/death and if lost to follow-up.
² Course 1 during radiation
³ Courses 2–4 subjects received oral etoposide and cisplatin
⁴ Courses 5–12 subjects received cyclophosphamide and vincristine
⁵ Sensory, motor and/or neuropathic pain.